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特発性大腿骨頭壊死症の関連要因に関する系統的レビュー（続報）

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新たな多施設共同症例・対照研究の実施に向けて、検討すべき要因を明確化するため、特発性大腿骨頭壊死症（ION）の関連要因に関する過去の報告について系統的レビューを行った。

2007年6月29日時点でPubMedに登録されていた論文から検索を行い、考慮すべき論文109編を選定した。このうち、「総てのION、あるいは非ステロイド性ION」の関連要因に関するレビュー結果は平成19年度に報告済みである。今年度は、「ステロイド性ION」に限定して関連要因を検討した論文35編についてレビューを行った。

報告の多くは、膠原病（SLEなど）や腎移植患者を対象としていた。以下、研究デザイン毎に概要を述べる。

比較研究は17編であった。約半数の研究がステロイド剤の投与量・投与法を評価しており、1日投与量、累積投与量、パルス療法有りで正の関連が報告されていた。その他の臨床情報でIONと正の関連が示唆されたものは、腎移植患者では移植後の拒絶反応やGVHD（移植片対宿主病）の出現、SLE患者では中枢神経系症状、偏頭痛、レイノー現象の存在であった。バイオマーカーでは、apolipoprotein(a)の低分子量、血清総コレステロール高値、白血球数高値、アルブミン高値、あるいはミダゾラムクリアランス低値でIONのリスク上昇が報告されていた。遺伝子関連では、ABCB1及びapolipoprotein Bの多型との関連が示唆されていた。

比較群を有しない観察研究、記述研究、および症例集積は15編であった。腎移植、骨髄移植、急性リンパ性白血病、自己免疫性疾患等に対してステロイド治療を受けた患者を対象に、 IONの発生頻度が調査されていた。また、40歳未満のION発生頻度が高いとする報告や、ステロイドとスタチンの併用投与によりIONの発生が低下することを示唆する報告もあった。

症例報告3編のうち、慢性の顔面湿疹に対して長期にわたり局所ステロイドを使用していた患者に発生した大腿骨頭壊死症が1例報告されていた。

現在、昨年度と今年度のレビュー結果をもとに、研究計画の立案および疫学情報・臨床情報の収集フォームの作成を進めている。

1. 研究目的

本研究班では、特発性大腿骨頭壊死症（ION）の発生要因解明を目的とした多施設共同症例・対照研究を過去3回にわたり実施してきた。第1回目の研究では、ステロイド全身投与歴を有しないION患者を症例とし、飲酒および喫煙の即時効果と累積効果を明らかにした。[1] 第2回目は、SLE患者あるいは腎移植患者を対象としてステロイド投与量・投与法の影響を詳細に検討し、1日平均投与量で最も鮮明な関連を認めることを示した。[2-4] 現在データ解析中の第3回目の研究では、誘因にかかわらず、総てのION患者を症例とすることで「ステロイド非投与に対する投与のリスク」を算出し、そのインパクトを明らかにした。[5]

一方、本研究班で運営している定点モニタリングシステム、あるいは2005年実施の全国疫学調査の集計結果によると、ステロイド全身投与歴およびアルコール多飲歴の両者を有しない症例が10%程度報告されている。[6,7] しかし現状では、ステロイド・アルコール以外の要因の影響について、十分な論拠が蓄積されていない。

以上の背景を考慮し、研究班として実施する第4回目の多施設共同症例・対照研究を計画している。新たな研究ではステロイド・アルコール以外の要因も幅広く調査することを予定しているため、検討すべき要因を明確化する必要がある。

今回、研究計画の立案に先立ち、IONの関連要因に関する過去の報告を網羅的に評価するための系統的

レビューを実施した。なお、「総ての ION、あるいは非ステロイド性ION」の関連要因に関するレビュー結果は昨年度に報告済みである。[8] 今年度は、「ステロイド性ION」に限定して関連要因を検討した論文についてレビューを行ったので、その結果を報告する。

2. 研究方法

2007 年 6 月 29 日時点で PubMed に登録されていた論文から検索を行った。Keyword は、[osteonecrosis AND femoral head AND (epidemiology OR risk OR characteristic)] とし、English で制限した。期間の制限は行わなかった。

検索された論文のうち、Title および Abstract から考慮すべきものを選定し、内容を一定のフォームにまとめた。

3. 研究結果

検索された論文は 452 編であった。このうち、①大腿骨頭壊死症に関する論文ではないもの、②動物実験によるもの、③病理所見、画像所見、治療、予後に関するもの、④対象者が症候性（二次性）大腿骨頭壊死症患者であるもの、を除外した 109 編をレビューの対象とした。

109 編の論文は、主たる研究目的に基づき、①総てのION、あるいは非ステロイド性ION の関連要因を検討したもの（70 編、うち 19 編が総説）、②ステロイド性 ION に限定して関連要因を検討したもの（39 編、うち 3 編が総説、1 編が comment to authors）、の 2 種類に大別した。本年度は、後者のうち、総説および comment to authors を除く 35 編についてレビューを行った。

報告の多くは、膠原病（SLE など）や腎移植患者を対象としていた。以下、研究デザイン毎に概要を述べる。

1）比較研究：17 編 （Table 1）

基本特性として、男性、アフリカ系アメリカ人でリスク上昇が報告されていた。年齢については、一貫した関連を認めなかった。

約半数の研究がステロイド剤の投与量・投与法を評価しており、1 日投与量、累積投与量、パルス療法有りについて正の関連が報告されていた。その他の臨床情報で ION と正の関連が示唆されたものは、腎移植患者では移植後の拒絶反応や GVHD（移植片対宿主病）の出現、SLE 患者では中枢神経系症状、偏頭痛、レイノー現象の存在であった。

バイオマーカーでは、apolipoprotein(a)の低分子量、血清総コレステロール高値、白血球数高値、アルブミン高値、あるいはミダゾラムクリアランス低値で ION のリスク上昇が報告されていた。遺伝子関連では、ABCB1 及び apolipoprotein B の多型との関連が示唆されていた。

その他、腎移植時にステロイドと併用する免疫抑制剤に着目し、シクロスポリン A と比較してタクロリムスの使用が有意に ION の発生を減少させるという報告があった。

2）比較群を有しない観察研究、記述研究、および症例集積：15 編 （Table 2）

腎移植、骨髄移植、急性リンパ性白血病、自己免疫性疾患等に対してステロイド治療を受けた患者を対象に、ION の発生頻度が調査されていた。また、40 歳未満の ION 発生頻度が高いとする報告や、ステロイドとスタチンの併用投与によりIONの発生が低下することを示唆する報告もあった。

3）症例報告：3 編 （Table 3）

放射線肺炎、精巣腫瘍、慢性の顔面湿疹に対するステロイド治療に関連すると考えられたION症例が報告されていた。そのうち、慢性の顔面湿疹に関する論文では、2 年 10 ヵ月の長期にわたり局所ステロイドを使用した患者に大腿骨頭壊死が発生していた。当該患者はその他のリスク要因を有していなかったため、局所ステロイドに関連した大腿骨頭壊死症例と考えられると報告されていた。

4. 考察および結論

昨年度と今年度のレビューにより、新たな症例・対照研究で検討すべき要因を把握することができた。

今後、これらの結果をもとに、研究計画の立案および疫学情報・臨床情報の収集フォームの作成を進める。

5. 研究発表

1. 論文発表
   なし
2. 学会発表
   なし

6. 知的所有権の取得状況

1. 特許の取得
   なし

2. 実用新案登録
   なし
3. その他
   なし

7. 参考文献

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6) 福島若葉, 廣田良夫, 藤岡幹浩, ほか：特発性大腿骨頭壊死症の全国疫学調査―最終結果―. 厚生労働科学研究費補助金難治性疾患克服研究事業 特発性大腿骨頭壊死症の予防と治療の標準化を目的とした総合研究 平成 18 年度総括･分担研究報告書, 1～6 頁, 2007.
7) 福島若葉, 田中 隆, 竹下節子, 廣田良夫, ほか. 定点モニタリングによる特発性大腿骨頭壊死症の記述疫学研究―新患症例に関する 8 年間の集計･確定診断年別の経年変化―. 厚生労働科学研究費補助金 難治性疾患克服研究事業 特発性大腿骨頭壊死症の予防と治療の標準化を目的とした総合研究 平成 16 年度総括･分担研究報告書, 6～10 頁, 2005.
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Table 1. Previous studies in relation to associated factors for steroidal ONFH (ONFH: osteonecrosis of the femoral head)

Study design: Comparison studies

Ref. No.	Authors/Year/Country	Study Design/Year/ Follow-up period	Subjects (M:male, F:female)	Mean (or median) age	Main result	
1	Hirata, et al 2007 Japan	Case-control 1983-2004	Case:34 (M:22/F:12) following renal transplantation and steroid use Control:124 (M:91/F:33) following renal transplantation and steroid use	39.5 35.0	Variables apolipoprotein B (C7623T) CT TT (vs CC) apolipoprotein B (G12619A) GA AA (vs GG) apolipoprotein A1 (G-75A) GA AA (vs GG) apolipoprotein A1 (C83T) CT TT (vs CC)	OR (95%CI) 6.37 (1.53 - 26.5) 0.55 (0.06 - 5.11) 1.41 (0.57 - 3.50) 1.39 (0.39 - 5.05)
					Variables HDL LDL LD/HDL ratio	P value 0.161 0.470 0.227
2	Hedri, et al 2007 Tunisia	Case-control 1986-2004	Case:15 (M:11/F:4) following renal transplantation and steroid use Control:15 following renal transplantation and steroid use mached for age, gender, date of renal transplantation	40.8 38.3	Variables Duration of dialysis (year) Mean rate of acute rejection episodes Cumulative mean dose of glucocorticoid Weight gain at 1 year after RT Serum creatinine	P value NS 0.058 0.04 NS NS
3	Hirata, et al 2007 Japan	Case-control 1983-2004	Case: 20 (gender ratio: unknown) following renal transplantation Control: 92 (gender ratio: unknown) following renal transplantation (unmatched)	unknown unknown	Variables Molecular weight phenotype of apolipoprotein A LMW (vs HMW)	OR (95%CI) 5.75 (1.76 - 18.74)
4	Kaneshiro, et al 2006 Japan	Case-control 2002-2006	Case: 26 (M: 53.8%) Control: 75 (M: 42.6%) unmatched	44.5±13.7 43.4±14.7	Variables Midazolam clearance <=9.5mL kg^{-1} min^{-1} (vs >9.5mL kg^{-1} min^{-1})	OR (95%CI) 9.08 (2.79 - 29.6)

Table 1 continues

Table 1. (continued)

Ref. No.	Authors/Year/Country	Study Design/Year/ Follow-up period	Subjects (M:male, F:female)	Mean (or median) age	Main result	
5	Talamo, et al 2005 US	Case-control 1998-	Case: 49 (M:38/F:11) with myeloma and dexamethasone treatment Control: 504 (M:290/F:214) unmatched	52.0 (SD:8.6) 58.0 (SD:9.85)	Variables Younger age Female Larger steroid dose unit/40mg	OR (95%CI) 0.962 (0.934 - 0.991) 0.392 (0.196 - 0.785) 1.028 (1.013 - 1.044)
6	Nagasawa, et al 2006 Japan	Case-control 1993-1998	60 newly diagnosed SLE patients requiring steroid therapy Warfarin (+) group: 31 (M:2/F:29) Warfarin (-) group: 29 (M:3/F:26) ↓ Case: 18 (M:4/F:14) Non-case: 42 (M:1/F:41)	30.2 (13 - 56) 29.8 (15 - 50) 30.8 29.7	Variables Male Steoid pulse therapy CNS disease	P value <0.05 <0.001 <0.05
7	Nagasawa, et al 2005 Japan	Case-control 1994-1997 (>5yrs follow-up)	Case: 15 (M:2/F:13) with SLE and high dose steroid therapy Control: 30 (F:30) with SLE and high dose steroid therapy	29.1 31.1	Variables Steoid pulse therapy (+) Total cholesterol ↑ WBC ↑ Albumin ↑	P value <0.05 <0.05 <0.05 <0.05
8	Asano, et al 2004 Japan	Case-control 1970-	Case: 31 (M:20/F:11) after renal transplantation Control: 106 (M:79/F:27) after renal transplantaiton unmatched	38.6 36.5	Variables PAI-1 genotype 4G/5G (vs 5G/5G) 4G/4G (vs 5G/5G) MTHFR genotype CT (vs CC) TT (vs CC)	OR (95%CI) 0.65 (0.17 - 2.47) 1.81 (0.48 - 6.78) 0.52 (0.20 - 1.39) 0.96 (0.30 - 3.08)
9	Inoue, et al 2003 Japan	Case-control 1983-1992	Case: 18 (M:11/F:7) after renal transplantation Control: 72 (M:51/F:21) after renal transplantation matched for age and gender	33.8 (20.4-56.2) 32.8 (19.0-61.2)	Variables BUN >= two-fold rise Steroid daily dosage >= 25.0mg	OR (95%CI) 2.17 (0.67 - 7.03) 7.06 (0.36 - 13.8)

Table 1 continues

Table 1. (continued)

Ref. No.	Authors/Year/Country	Study Design/Year/ Follow-up period	Subjects (M:male, F:female)	Mean (or median) age	Main result	
10	Sakai, et al 2003 Japan	Cohort -	Cyclosporin A: 32 (M:21/F:11) Tacrolimus: 32 (M:21/F:11) matched for age, gender, and renal allograft	35.1±9.4 35.3±10.1	Osteonecrosis: 5 Osteonecrosis: 0	P value 0.026
11	Asano, et al 2003 Japan	Case-control 1970-	Case: 30 (M:20/F:10) after renal transplantation Control: 106 (M:78/F:28) after renal transplantation	40.5 (25-63) 36.2 (9-62)	Variables ABCB1 genotype 3435TT (vs 3435CC or CT) 2677(TorA)(TorA) (vs 2677GG or G(TotA))	OR (95%CI) 0.10 (0.01 - 0.84) 0.30 (0.09 - 0.98)
12	Asano, et al 2003 Japan	Case-control 1970-	Case: 26 (gender ratio: unknown) after renal transplantation Control: 54 (gender ratio: unknown) after renal transplantation unmatched	unknown unknown	Variables CYP2D6 IM (vs EM) CYP2C19 PM (vs EM)	OR (95%CI) 1.8 (0.4 - 7.9) 1.0 (0.2 - 6.8)
13	Torii, et al 2001 Japan	Case-control 1981-1998	Case: 19 (M:10/F:9) after bone marrow transplantation Control: 81 (M:45/F:36) after bone marrow transplantation	28.6±7.85 34.2±10.4	Variables Age (10 years increment) Chronic GVHD (Yes/No) Pulse regimen (Yes/No)	OR (95%CI) 0.47 (0.234 - 0.934) 5.57 (1.032 - 30.1) 11.3 (3.15 - 40.44)
14	Lausten, et al 1998 Denmark	Cohort 1968-1995	High-dose steroid: 374 (M:206/F:168) Low-dose steroid: 376 (M:239/F:137) after a kidney transplantation	43 (6-66) 48 (7-76)	11.2% (42/374, average of 26.2 months after transplantation) 5.1% (19/376, average of 20.5 months after transplantation)) P=0.002	
15	Aranow, et al 1997 US	Case-control -	66 patients with SLE and steroid treatment (M:5/F:61) Case: 8 Control: 58	34.9 (18-67)	Variables African-American origin Predonisone (>30mg/day) Migraine headache Raynaud's phenomenone	OR (95%CI) 11.5 (7.3 - 18.0) 4.2 (2.5 - 6.9) 3.5 (2.2 - 5.4) 1.8 (1.1 - 2.8)

Table 1 continues

Table 1. (continued)

Ref. No.	Authors/Year/Country	Study Design/Year/ Follow-up period	Subjects (M:male, F:female)	Mean (or median) age	Main result	
16	Saisu, et al 1996 Japan	Case-control 1974-1994	Case: 22 (M:17/F:5) after renal transplantations Control: 47 (M:33/F:14) after renal transplantations	31.0 (SD=8.7) 29.8 (SD=7.7)	Variables Intravenous pulse dose of methylprednisolone Maintenace dose of prednisolone	P value 0.0009 0.0012
			After 1982 (after introduce of cyclosporin A) Case: 12 after renal transplantations Control: 44 after renal transplantations	 - -	Variables Intravenous pulse dose of methylprednisolone Maintenace dose of prednisolone	P value 0.0013 NS
17	Lausten, et al 1988 Denmark	Cohort Case-control 1968-1987	Patients with renal transplantations Prednisone+Azathioprine: 374 (M:206) CyclosporinA+reduced steroid: 124 (M:69)	 - -	 ONFH 42/374 ONFH 4/124 (P<0.01)	
			Case: 46 Control: 46 matched for age, sex, number of transplantation, f/u time		Variables Patients with rejection (ION+: 22, ION-:35)	P value <0.05